IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:		
Malcolm J. Simons	Examiner:	Sisson, Bradley L.
Application No: 09/935,998	Art Unit:	1634
Filed: August 23, 2001		
For: Intron Sequence Analysis Method for Detection of Adjacent and Remote Locus Alleles as Haplotypes		

APPEAL BRIEF IN SUPPORT OF APPELLANT'S APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

Sir:

Applicant Genetic Technologies Limited (hereafter "Appellant") hereby submits this Brief in triplicate in support of its appeal from a decision by the Examiner, mailed March 31, 2004, in the above-referenced application. Appellant respectfully requests consideration of this Appeal by the Board of Patent Appeals and Interferences (the "Board") for allowance of the above-captioned patent application.

On June 30, 2004, Appellant filed a Notice of Appeal for the present application. The claims of the present application were finally rejected by the Examiner in a final Office Action mailed March 31, 2004 (the "**Final Action**"). Therefore, this is a proper Appeal and Appellant's Brief in support of this Appeal follows.

REAL PARTY IN INTEREST

The real party in interest in this Appeal is Genetic Technologies Limited of 60-66 Hanover Street, Fitzroy, Victoria 3065, Australia, the assignee of a 100% interest in U.S. Patent Application Serial No. 09/935,998, by virtue of an assignment from GeneType AG to Genetic Technologies Limited executed on November 7, 2002, and recorded at reel/frame 013577/0720. GeneType AG had previously been assigned a 100% interest in USSN 09/935,998 by virtue of an assignment in the grandparent application USSN 07/551,239, of which USSN 09/935,998 is a continuation, from the sole inventor, Dr. Malcolm J. Simons, to GeneType AG recorded at reel/frame 005423/0553.

RELATED APPEALS AND INTERFERENCES

There are no known appeals or interferences related to this Appeal.

STATUS OF CLAIMS

Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 are currently pending in the above-referenced application. The Final Office Action rejected all pending claims under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Final Office Action also rejected all pending claims under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Final Office Action rejected all pending claims under 35 U.S.C. § 112, second paragraph as being indefinite. The Final Office Action also rejected all pending claims under 35 U.S.C. § 103 as obvious over U.S. Patent No. 4,582,788 to Erlich (hereafter "Erlich") in view of EP 0256630 to Woo et al. (hereafter "Woo et al.")

Claims 1-3, 5-9, 11-15, 17-21, 23 and 25-30 as set forth in the Amendment, dated October 1, 2003, are the subject of this Appeal. Appendix A below sets forth a copy of the appealed claims.

STATUS OF AMENDMENTS

An amendment after final Office Action was submitted on June 30, 2004. An Advisory Action mailed on July 16, 2004 declined to enter the proposed amendment. A copy of all claims on appeal is attached hereto in Appendix A.

SUMMARY OF INVENTION

The above-captioned patent application generally relates to the use of non-coding sequence variants to determine at least one haplotype encompassing a human leukocyte antigen (HLA) locus. (Spec. at pg. 6, lines 16-19; pg. 7, lines 9-11) The application is based on the discovery that non-coding regions of chromosomes are informative for determining haplotypes of loci that are in genetic linkage with the non-coding regions. (Spec. at pg. 6, lines 16-32)

ISSUES

A. Is the Rejection of the Claims under 35 U.S.C. § 112, 1st Paragraph as Failing to Comply with the Written Description Requirement Based on a Flawed Construction of Claim Scope?

B. Is the Rejection of the Claims under 35 U.S.C. § 112, 1st Paragraph as Failing to Comply with the Enablement Requirement Based on a Flawed Construction of Claim Scope?

C. Is the meaning of the claims clear to a person of ordinary skill in the art?

D. Did the Examiner fail to establish a *prima facie* case of obviousness?

GROUPING OF CLAIMS

In view of the issues presented and for purposes of this Appeal, Appellant groups the claims on appeal as follows:

Group I: Claims 1-3, 5-9, 11-15, 17-20, 23, 25 and 29-30

With respect to the claims of Group I, the claims stand or fall together.

ARGUMENT

A. The Rejection of the Claims under 35 U.S.C. § 112, 1st Paragraph as Failing to Comply with the Written Description Requirement is Based on an Improper Construction of Claim Scope.

The Final Office Action rejected the pending claims under 35 U.S.C. § 112, 1st paragraph as failing to comply with the written description requirement. As discussed in the Response to Final Action filed by facsimile on June 30, 2004, Applicant asserts that the above rejection under 35 U.S.C. § 112, 1st paragraph is based on a faulty construction of the claim scope.

Claim construction analysis begins with the words of the claims. [*See Vitronics Corp. v. Conceptrionic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)] "In construing claims, the analytical focus must begin and remain centered on the language of the claims themselves." [*Nystrom v. Trex Company, Inc.*, No. 031092v2 – 06/28/04 (Fed. Cir. 2004), citing *Ferguson Beauregard v. Mega Sys., Inc.*, 350 F.3d 1327, 1338 (Fed. Cir. 2003)] "In the absence of an express intent to impart a novel meaning to claim terms, an inventor's claim terms take on their ordinary meaning .... [T]he ordinary meaning must be determined from the standpoint of a person of ordinary skill in the relevant art." [*Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed. Cir. 2002)] During patent examination, pending claims are given their broadest reasonable interpretation consistent with the specification. [*In re Hyatt*, 211 F.3d, 1367, 1372 (Fed. Cir. 2000)] However, the broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach. [*In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999)]

1. The Interpretation Encompassing Amplification of Entire Chromosome 6 is Unreasonable

The Final Action stated that, "For the purposes of examination, the phrase 'genetic linkage' has been interpreted as encompassing the entire chromosome upon which the HLA complex is found (chromosome 6). Accordingly, claims 1, 13, and 19 have been interpreted as encompassing amplification of entire chromosome 6." [Final Action at ¶ 10] The Final Action stated that the specification fails to disclose an adequate written description of the claimed methods, "where amplicons of any length are to be generated." [Final Action at ¶ 14] Appellant respectfully asserts that one of skill in the art would not have considered the interpretation encompassing the amplification of the entire chromosome 6 to be reasonable, in light of the claim language and specification.

It was well known in the art as of the date of the present application that chromosomes are millions of basepairs in length. In fact, chromosome 6, on which the HLA loci are found, is over 170,000,000 basepairs in length (see, *e.g.,* NCBI Map Viewer, *Homo sapiens*, Chromosome 6, www.ncbi.nlm.nih/gov/mapview/). Given the size of the entire chromosome 6, no skilled artisan would have considered it reasonable to interpret the claims to require amplification of the entire 170,000,000 basepair sequence.

That interpretation is unsupported by the claim language and the specification. The text of Claim 1 of the pending application is cited below:

Claim 1. A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

The Final Action focuses on the use of the term "genetic linkage" and asserts that the entire chromosome 6 may be in genetic linkage with the HLA loci. However, the Final Action

completely ignores the first part of element (a), which recites, "amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence...." The phrase "amplifying human genomic DNA" requires that the sequence to be amplified must be amplifiable. This is further emphasized by reference to an "amplified genomic DNA" that results. Since a 170 million basepair (Mbp) sequence is not amplifiable, there could be no amplified genomic DNA encompassing all of chromosome 6.

As noted in previous Office Actions, the specification contains numerous references to amplified sequences, that are nowhere near 170 Mbp in size. For example: pg. 14, lines 9-11, ("Exon-limited primers can be used to produce an amplified sequence that includes as few as about 200 nucleotides..."); pg. 14, lines 31-32 ("About 300 to 500 nucleotides is sufficient..."); pg. 15, lines 11-14 ("The amplified sequences used to characterize highly polymorphic loci are generally between about 800 to about 2,000 nucleotides..."); pg. 17, lines 28-29 ("Since PCR methodology can be used to amplify sequences of several Kb"). The specification discloses at pages 57 to 64 a number of exemplary primer pairs for amplification of various HLA loci sequences. Those generally would result in amplified sequences from slightly over one hundred to less than two thousand basepairs in length, although an amplified sequence as short as 53 basepairs in size is disclosed in the Examples (pg. 89, lines 27-29, shortest amplicon disclosed equals 207 minus 154, *i.e.,* 53 nucleotides).

Nowhere does the specification disclose an amplified DNA sequence even approaching 170 Mbp in size. Rather, the specification consistently recites amplified sequences ranging from about 50 to about 2,000 basepairs in size. Given the disclosure in the specification and the knowledge in the art, Appellant reiterates that no skilled artisan could reasonably interpret the scope of the claims to encompass "amplification of entire chromosome 6".

The Final Action's interpretation of claim scope is also inconsistent with other claim language. Claim 1 recites that one or more non-coding region sequence variations are detected "to determine at least one haplotype encompassing the HLA locus." The specification defines "haplotype" at pg. 9, lines 22-28 as:

> ...a region of genomic DNA on a chromosome which is bounded by recombination sites such that genetic loci within a haplotypic region are usually inherited as a unit. However, occasionally, genetic rearrangements may occur

within a haplotype. Thus, the term haplotype is an operational term that refers to the occurrence on a chromosome of linked loci.

It is clear that haplotypes occur on regions of chromosomal DNA that are bounded by recombination sites. Thus, the non-coding sequence variations that are of use to determine haplotypes are those that occur within the same haplotypic region as the haplotype to be determined. As such haplotypic regions do not extend over the entire chromosome 6, it is unreasonable to construe the scope of the claimed subject matter to "encompass amplification of entire chromosome 6."

As the rejection of the pending claims for failure to comply with the written description requirement is based upon an unreasonable construction of the claims, Appellant asserts that the rejection is improper. Given the disclosure of numerous exemplary embodiments in the specification of amplified sequences of a range of amplifiable sizes, Appellant asserts that the instant application provides ample written description support commensurate with the properly construed scope of the claims.

2. The Interpretation Encompassing the Simultaneous Amplification and Analysis of at Least 50 Different Loci is Unreasonable

The Final Action states that, "The claims have been interpreted as encompassing the amplification of all the loci, known and unknown, in a simultaneous manner, and wherein the amplicons for each of the loci is of like size and is similarly labeled as with any other amplicon for different loci." The Final Action further refers to the disclosure in the specification that the HLA complex comprises "'at least 50 loci.' Accordingly, the claimed method is considered to fairly encompass the simultaneous amplification and analysis of at least 50 different loci." [Final Action at ¶ 11]

Appellant reiterates that the Final Action's interpretation of claim scope is not reasonable. Nowhere does the claim language or specification support an interpretation that the claims cover the simultaneous amplification and analysis of at least 50 different loci. Claim 1 recites, "amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus; detecting one or more sequence variations in the non-coding region; and using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the

human HLA genetic coding locus." On its face, the language refers to "an HLA genetic coding locus" and determining "at least one haplotype encompassing the HLA genetic coding locus."

In support of its interpretation, the Final Action cites the language of claims 3, 15 and 21 to "two or more haplotypes are determined." Claim 1(c) recites, "using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the HLA locus." It is clear from that language that the at least one (i.e., one or more) haplotypes encompass the HLA locus. This language reflects the possibility that a given HLA locus may exhibit multiple haplotypes in a population. The specification at pg. 2, lines 29-33 discloses that the majority of HLA loci were known to be polymorphic and would therefore exhibit multiple haplotypes within a population. At a minimum, chromosomal DNA from a given individual may exhibit two different haplotypes at a given HLA locus, as there would be two copies of each HLA gene present – one inherited from the mother and one from the father. Unless both parental chromosomes have identical haplotypes, a given HLA locus in DNA obtained from one individual would exhibit two different haplotypes.

The specification further discloses that the amplification, detection of non-coding sequence variations and determination of haplotype(s) may not result in the determination of a unique haplotype. Rather, analysis of HLA loci haplotypes may be of use where the haplotype(s) may be determined to belong to one of a group of possible haplotypes.

For example, the specification at pg. 74, lines 2-7 states that:

> Carriers of genetic diseases and those affected by the disease can be identified by use of the present method. Depending on the disease, the screening analysis can be used to detect the presence of one or more alleles associated with the disease or the presence of **haplotypes** associated with the disease. (emphasis added)

That is, the claimed methods are not limited to the determination of a unique haplotype encompassing an HLA locus, but rather may result in the determination of multiple haplotypes, such as those associated with a disease.

The specification discusses the cystic fibrosis (CF) locus as an example of a disease-associated locus. The specification states that:

> Studies of haplotypes of parents of CF patients (who necessarily have one normal and one disease-associated haplotype) indicated that there are at least 178 haplotypes associated with the CF locus. Of those haplotypes, 90 are associated only with the disease; 78 are found only in normals; and 10 are associated with both the disease and with normals (Kerem et al., supra). The disease apparently is caused by several different mutations, some in very low frequency in the population. As demonstrated by the haplotype information, there are more haplotypes associated with the locus than there are mutant alleles responsible for the disease.
>
> A genetic screening program (based on amplification of exon regions and analysis of the resultant amplified DNA sequence with probes specific for each of the mutations or with enzymes producing RFLP patterns characteristic of each mutation) may take years to develop. Such tests would depend on detection and characterization of each of the mutations, or at least of mutations causing about 90 to 95% or more of the cases of the disease. The alternative is to detect only 70 to 80% of the CF-associated genes. That alternative is generally considered unacceptable and is the cause of much concern in the scientific community.
>
> The present method directly determines haplotypes associated with the locus and can detect haplotypes among the 178 currently recognized haplotypes associated with the disease locus.

The skilled artisan, reading the claims in light of the specification, would conclude that the phrase, "to determine at least one haplotype encompassing the HLA locus" refers to determining one or more possible haplotypes encompassing an HLA locus, not to "the amplification of all the loci, known and unknown, in a simultaneous manner, and wherein the amplicons for each of the loci is of like size and is similarly labeled as with any other amplicon for different loci" or to "the simultaneous amplification and analysis of at least 50 different loci" as asserted by the Final Action.

As discussed above, because the § 112 written description rejection is based on an unreasonable interpretation of claim scope, Appellant asserts that the rejection is improper. The specification discloses the amplification, analysis and determination of haplotypes for numerous exemplary HLA loci, commensurate with the properly construed scope of the claims. Appellant thus asserts that there is ample written description support in the specification for the pending claims.

3. The Final Action Fails to Establish a Prima Facie Case for Lack of Written Description of Primers of Any Length

There is a strong presumption that an adequate written description of a claimed invention is present in the specification as filed. [MPEP § 2163.03, citing *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976)] In order to support a *prima facie* case of lack of written description, the Examiner bears the initial burden of presenting, by a preponderance of the evidence, reasons why a person skilled in the art would not recognize a description of the invention defined by the claims. [MPEP § 2163, citing *Wertheim*, 541 F.2d at 263] For the reasons discussed below, Appellant asserts that the Examiner has failed to establish a *prima facie* case of lack of written description.

The Final Action states that the claimed methods, "have also been interpreted as encompassing the use of any length and combination of primer..." [Final Action at ¶ 13] "A review of the specification fails to find an adequate description of the claimed methods wherein primers of any length are to be used..." [Final Action at ¶ 14] "Attention is also directed to page 22 of the disclosure where it is taught that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides. Accordingly, the specification does not reasonably support the position that [Appellant] contemplated, much less possessed, methods where primers of lengths outside of 8 to 30 nucleotides were to be used..."

Appellant initially notes that page 22 of the specification does not appear to support the assertion that "[it] is taught that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides." For convenience, the cited section of the specification is reproduced below.

> Each locus-specific primer includes a number of nucleotides which, under the conditions used in the hybridization, are sufficient to hybridize with an allele of the locus to be amplified and to be free from hybridization with alleles of other loci. The specificity of the primer increases with the number of nucleotides in its sequence under conditions that provide the same stringency. Therefore, longer primers are desirable. Sequences with fewer than 15 nucleotides are less certain to be specific for a particular locus. That is, sequences with fewer than 15 nucleotides are more likely to be present in a portion of the DNA associated with other genetic loci, particularly loci of other common origin or evolutionarily closely related origin, in inverse proportion to the length of the nucleotide sequence.

> Each primer preferably includes at least about 15 nucleotides, more preferably at least about 20 nucleotides. The primer preferably does not exceed about 30 nucleotides, more preferably about 25 nucleotides. Most preferably, the primers have between about 20 and about 25 nucleotides.
>
> A number of preferred primers are described herein. Each of those primers hybridizes with at least about 15 consecutive nucleotides of the designated region of the allele sequence. For many of the primers, the sequence is not identical for all of the other alleles of the locus. For each of the primers, additional preferred primers have sequences which correspond to the sequences of the homologous region of other alleles of the locus or to their complements.
>
> When two sets of primer pairs are used sequentially, with the second primer pair amplifying the product of the first primer pair, the primers can be the same size as those used for the first amplification. However, smaller primers can be used in the second amplification and provide the requisite specificity. These smaller primers can be selected to be allele-specific, if desired. The primers of the second primer pair can have 15 or fewer, preferably 8 to 12, more preferably 8 to 10 nucleotides. When two sets of primer pairs are used to produce two amplified sequences, the second amplified DNA sequence is used in the subsequent analysis of genetic variation and must meet the requirements discussed previously for the amplified DNA sequence.

It is clear from the text of the Specification that the Final Action's assertion, "that the primers used in the claimed methods are to range in size from 8 to 30 nucleotides" represents a preferred embodiment. Thus, "The primers of the second primer pair can have 15 or fewer, preferably 8 to 12, more preferably 8 to 10 nucleotides" Also, "The primer preferably does not exceed about 30 nucleotides..." There is no basis in the specification or the claim language to attempt to limit the claimed subject matter to the disclosed preferred embodiments.

The specification states that, "Each locus-specific primer includes a number of nucleotides which, under the conditions used in the hybridization, are sufficient to hybridize with an allele of the locus to be amplified and to be free from hybridization with alleles of other loci." There is no explicit size limit expressed concerning the primers of use in the claimed methods. The only stated requirement [for locus specific primers] is that the primers include a sufficient number of nucleotides to hybridize with the locus to be amplified and not to other loci.

As of the date of the instant application, it was well known in the art how to make and use primers. The specification provides guidance to the skilled artisan as to exemplary methods for primer preparation. For example, at pg. 23, lines 20-33:

> The primers can be prepared using a number of methods, such as, for example, the phosphotriester and phosphodiester methods or automated embodiments thereof. The phosphodiester and phosphotriester methods are described in Cruthers, Science 230:281-285 (1985); Brown et al, Meth. Enzymol., 68:109 (1979); and Nrang et al, Meth. Enzymol., 68:90 (1979). In one automated method, diethylphosphoramidites which can be synthesized as described by Beaucage et al., Tetrahedron letters, 22:1859-1962 (1981) are used as starting materials. A method for synthesizing primer oligonucleotide sequences on a modified solid support is described in U.S. Pat. No. 4,458,066.

The exemplary methods recited above are not limited to primers of between 8 and 30 nucleotides in length. Rather, using such methods, primers of a wide range of lengths may be prepared. The specification at pages 57-64, 83 and 89-93 discloses a large number of exemplary primers of different sizes.

The written description requirement does not require that the claimed subject matter be described *in haec verba* (i.e., using the same terms) in order to satisfy the written description requirement. [MPEP §2163.02] Appellant respectfully asserts that, given the ample disclosure in the specification of numerous exemplary embodiments within the scope of the claimed subject matter, the skilled artisan would recognize that the instant inventor had invented the claimed subject matter, without limitation as to the size of the primers used. [*See, e.g., In re Gosteli,* 872 F.2d 1008, 1012 (Fed. Cir. 1989)]

4. The Specification Contains Written Description Support for a Representative Number of Species of the Genus of HLA Loci

The Final Action at pg. 7, ¶ 14 states that, "While the specification does provide a description of analyzing the HLA DQA1 locus in humans, the specification has not been found to provide the requisite description of such a broad genus as claimed." The written description requirement for a genus claim may be satisfied through sufficient description of a representative number of species. [MPEP § 2163, citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)] A 'representative number of species' means that the species are representative of the entire genus. [MPEP § 2163] Disclosure of a single species within a genus may provide adequate written description support for the genus. [*e.g., In re Herschler,* 591 F.2d 693, 697 (CCPA 1979)] "Description of a representative number of species

does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." [MPEP § 2163]

The Final Action at ¶16 acknowledges that the Specification provides primers for the HLA-A, HLA-B, HLA-C, DQA1, DRA, DRB, DQB1 and DPB1 loci. The Specification at pg. 2, lines 25-30 states that for the purpose of HLA tissue typing, two main classes of loci are recognized – the Class I loci (A, B and C) and the Class II loci (DRA, DRB, DQA1, DQB, DPA and DPB). U.S. Patent No. 4,582,788 (Erlich) states that, "The major histocompatibility complex (MHC) of humans is a cluster of genes occupying a region located on the sixth chromosome. This complex, denoted HLA (Human Leukocyte Antigen), has been divided into five major gene loci, which according to World Health Organization nomenclature are designated HLA-A, HLA-B, HLA-C, HLA-D and HLA-DR. The A, B, and C loci are single gene loci. The D and DR loci are multi-gene loci." According to U.S. Patent No. 6,194,147 (Baxter-Lowe *et al.*), "The major histocompatibility complex of humans (denoted HLA—human leukocyte antigen) is a cluster of genes occupying a region located on the sixth chromosome. The polymorphic proteins encoded by the HLA region have been designated HLA-A, -B, -C, -DR, -DQ, and -DP...D-region proteins are encoded by loci designated DRA, DRB1, DRB3, BRB4, DQA1, DQB1, DPA1, and DPB1."

Appellant respectfully asserts that the Specification discloses a representative number of species, including representatives of each of the major HLA gene loci known as of the priority date of the instant application, in satisfaction of the written description requirement for the genus of HLA loci.

5. The Specification Contains Written Description for Determining Haplotypes Encompassing HLA Loci

The Final Action at ¶ 17 asserts that, "the specification is essentially silent as to which mutations for any and all HLA loci are to be correlated, directly and indirectly, with any disease (claims 5 and 17)...the specification is silent as to how one is to identify useful mutations from useless mutations when the disease is multigenic in origin and the genes, much less the mutation involved in causing the disease, are not known". However, the claims do not require correlation of specific mutations with a disease state. To reiterate, Claim 1 concerns a method for determining at least one haplotype encompassing a human HLA genetic locus. It says nothing

about determining specific mutations correlated with a disease. Claim 5 recites the method of Claim 1, wherein the haplotype is associated with a disease. Again, it says nothing about determining specific mutations correlated with the disease.

The Specification provides detailed instructions for how to determine haplotypes by several different analytical methods. It provides specific, non-limiting examples of haplotype determination, such as Examples 3 and 4 for the HLA-DQA1 locus. Methods for determining haplotypes associated with a disease are disclosed in the Specification at pages 74-78. The Specification explicitly states that, "neither the mutation site nor the location for a disease gene is required to determine haplotypes associated with the disease. Amplified intron sequences in the regions of closely flanking RFLP markers, such as are known for Huntington's disease and many other inherited diseases, can provide sufficient information to screen for haplotypes associated with the disease."

The Final Action's argument for lack of written description is based on a limitation that is not present in any of the claims. Adequate written description support is provided for the claimed subject matter of determining haplotypes encompassing HLA loci.

B. The Rejection of the Claims under 35 U.S.C. § 112, 1st Paragraph as Failing to Comply with the Enablement Requirement is Based on an Improper Construction of Claim Scope.

The Final Action at ¶ 21 asserts that the claims lack enablement, "as one cannot enable that which they do not have possession of." As discussed above, the rejection for lack of written description support was based on an incorrect construction of the claims. Because there is adequate written description support for the properly construed scope of the claims, the enablement rejection based on lack of written description support is improper.

1. Amplification Methods Were Well Known in the Art and Fully Enabled by the Specification

Paragraph 22 of the Final Action refers to "amplification artifacts due to error on the part of the polymerase as well as because of mis-priming, including primer-dimer formation." That paragraph also refers to the claimed method encompassing "any number of amplification steps" and using "any level of stringency".

Various amplification techniques, such as PCR amplification, were well known in the art as of the priority date of the instant application. For example, U.S. Patent No. 4,683,195 (Mullis, attached as Appendix B), incorporated by reference into the instant application, provided a detailed description of the PCR process, including primer selection and synthesis and hybridization conditions suitable for general use in PCR amplification. The Mullis reference covered the various factors cited in ¶ 22, such as incubation temperature, ionic strength, incubation time, denaturing reagents, base composition, *etc.*, all of which were well known in the art. U.S. Patent No. 4,683,194 (Saiki et al., attached as Appendix C), also incorporated by reference into the instant application, provided additional details on amplification and hybridization techniques.

Such general techniques were known to those of skill in the art. The skilled artisan was specifically directed to those and other references on amplification techniques at pages 24-30 of the Specification, which provided additional guidance to the artisan on various techniques, such as genomic DNA purification, hybridization conditions (*e.g.*, ionic strength, pH, temperature and time of incubation) and amplification methods. Particular non-limiting examples of conditions of use for amplification were disclosed in Examples 1-8. For instance, Example 1 recites:

> The extracted DNA from each sample is used to form two replicate aliquots per sample, each aliquot having 1 .mu.g of sample DNA. Each replicate is combined in a total volume of 100 .mu.l with a primer pair (1 .mu.g of each primer), dNTPs (2.5 mM each) and 2.5 units of Taq polymerase in amplification buffer (50 mM KCl; 10 mM Tris-HCl, pH 8.0; 2.5 mM MgCl.sub.2 ; 100 .mu.g/ml gelatin) to form four amplification reaction mixtures. The first primer pair contains the primers designated SGD005.IIVS1.LNP and SGD009.AIVS3.R2NP (A locus-specific). The second primer pair contains the primers designated SGD001.DQA1.LNP and SGD003.DQA1.RNP (DQA locus-specific). Each primer is synthesized using an Applied Biosystems model 308A DNA synthesizer. The amplification reaction mixtures are designated SA (suspect's DNA, A locus-specific primers), SD (suspect's DNA, DQA1 locus-specific primers), CA (crime scene DNA, A locus-specific primers) and CD (crime scene DNA, DQA1 locus-specific primers).
>
> Each amplification reaction mixture is heated to 94.degree. C. for 30 seconds. The primers are annealed to the sample DNA by cooling the reaction mixtures to 65.degree. C. for each of the A locus-specific amplification mixtures and to 55.degree. C. for each of the DQA1 locus-specific amplification mixtures and maintaining the respective temperatures for one minute. The primer extension step is performed by heating each of the amplification mixtures to 72.degree. C.

for one minute. The denaturation, annealing and extension cycle is repeated 30 times for each amplification mixture.

That level of detail is more than sufficient to guide the skilled artisan in how to use the claimed methods. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." [MPEP 2164.01(b), citing *In re Fisher*, 427 F.2d 833, 839 (CCPA, 1970)] Given the ample guidance in the Specification and the extensive general knowledge in the art (*e.g.*, U.S. Patent No. 4,683,195), it would have been a matter of routine experimentation for the skilled artisan to select, design and implement primers and amplification conditions for any known locus as of the instant application's priority date. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." [MPEP § 2164.01, citing *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n, 1983)] Appellant submits that modification of factors such as primer sequence, salt concentration, temperature, denaturing agents, *etc.*, were typically engaged in by those practicing amplification techniques.

2. The Asserted "Art-Recognized Issue" With Amplification of HLA Loci is Not Relevant to the Instant Claims

Paragraphs 23 and 24 of the Final Action cite the references of Canck *et al.* (U.S. 2002/0197613 A1) and Baxter-Lowe *et al.* (6,194,147) to assert that there were art-recognized issues with amplifying HLA loci. Appellant initially notes that neither of those references was available as of the instant application's priority date. This appears to conflict with the requirement that the specification must be enabling as of the application's filing date. [MPEP § 2164.05] "Whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art." [*Id.*] "The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed." [*Id.*] Thus, it is clear that enablement is to be judged as of the application's filing (or priority)

date, against the backdrop of the knowledge and skill in the art as of that date. "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." [*Id.*]

This is not a situation in which a later publication states that a claimed invention could not be achieved. In fact, both of the cited publications claim methods for HLA typing by PCR amplification, thus acknowledging that PCR amplification of HLA loci is possible.

The citation to Canck *et al.*, is inappropriate, as that reference concerned HLA typing by analyzing exon sequences of the HLA loci. The claimed methods of the instant application concern haplotyping of HLA loci by examining non-coding region sequences. The Specification makes clear that because non-coding regions are more informative than coding regions, the length of amplified sequences needed is shorter. For example:

> Addition of invariant exon sequences provides no additional genetic variation. When about eight or more alleles are to be distinguished, as for the DQA1 locus and more variable loci, amplified sequences should extend into at least one intron in the locus, preferably an intron adjacent to the variable exon.
>
> Additionally, where alleles of the locus exist which differ by a single basepair in the variable exon, intron sequences are included in amplified sequences to provide sufficient variability to distinguish alleles. For example, for the DQA1 locus (with eight currently recognized alleles) and the DPB locus (with 24 alleles), the DQA1.1/1.2 (now referred to as DQA1 0101/0102) and DPB2.1/4.2 (now referred to as DPB0201/0402) alleles differ by a single basepair. To distinguish those alleles, amplified sequences which include an intron sequence region are required. About 300 to 500 nucleotides is sufficient, depending on the location of the sequence. That is, 300 to 500 nucleotides comprised primarily of intron sequence nucleotides sufficiently close to the variable exon are sufficient. [Specification at pg. 14, lines 15-35]

It is because the method of Canck *et al.*, is directed to analysis of variations in exon sequences that it requires amplification of large, difficult to amplify amplicons. This point is emphasized in the passage cited by the Examiner:

> In addition, due to the emergence of new HLA-Class I alleles, certain allele combinations cannot be distinguished anymore by the detection of polymorphisms only in exon 2 and exon 3 and additional typing in exon 4 is required. This raises the need for the additional amplification of exon 4, resulting in an even larger amplicon. (Final Action at ¶23, emphasis added)

The cited passage refers to HLA typing only by analyzing polymorphisms in exons, not in non-coding regions. If anything, the disclosure of Canck *et al.* points out the novelty, utility and advantage of the instant claimed methods. To use the difficulties of Canck *et al.* in amplifying large exon sequences to infer that the shorter amplified non-coding region sequences of the instant claims would require undue experimentation is unjustified and inappropriate. Because the instant claimed methods utilize the higher information content present in non-coding sequences to determine haplotypes, they do not require amplification of large target sequences that are needed for analysis based solely on exon sequences. While the claimed methods do not exclude analysis of coding region sequences in addition to non-coding region sequences, the use of the non-coding sequences allows amplification and analysis of shorter amplicons than an exclusively exon-based analysis.

The Final Action's reliance on Baxter-Lowe *et al.* (U.S. 6,194,147) is similarly misplaced, as that reference also discloses probe sequences based on coding region polymorphisms, not non-coding ones. Table 3 of Baxter-Lowe clearly shows that the probe sequences used were designed to bind to coding regions, since that Table also provides the amino acid sequences encoded by the probes. The difficulty of using coding region probes for HLA typing is emphasized by the instant Specification at pg. 14, lines 21-24:

> Additionally, where alleles of the locus exist which differ by a single basepair in the variable exon, intron sequences are included in the amplified sequences to provide sufficient variability to distinguish alleles.

It is precisely that limited variability in exon sequences that is posed as a problem by Baxter-Lowe:

> Some of these sequences are closely similar, and vary by as little as a single nucleotide. The need for a typing method which can identify single nucleotide differences at single locations is apparent, although it should not be necessary to detect silent changes, i.e., mismatches which do not change the resulting amino acid. (6,194,147, col. 11, lines 39-45)

It is because the methods of Canck *et al.* and Baxter-Lowe *et al.* are targeted at coding region sequence variations that they encountered difficulties. Because the instant claimed methods concern analysis of highly informative non-coding region sequences, the difficulties of analyzing very similar coding region sequences are overcome. For that reason, it is inappropriate

to assert a lack of enablement of the instant application, based upon the non-analogous methods utilized by Canck and Baxter-Lowe.

C. The Meaning of the Claims is Clear to a Person of Ordinary Skill in the Art

A response after Final Action was filed on June 30, 2004, to comply with requirements of form and to reduce the number of issues on appeal. Claim amendments were proposed to address each of the § 112, second paragraph issues raised by the Final Action. Specifically, Claims 1, 13 and 19 were amended to recite "human leukocyte antigen" followed by the abbreviation "(HLA)". Claims 1, 13 and 19 were amended to delete "genetic coding" from the phrase "HLA genetic coding locus". Claim 8 was amended to recite "a coding region of the locus" instead of "the coding region of the locus." An Advisory Action mailed on July 16, 2004, refused entry of all proposed amendments because, "they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal." Appellant respectfully suggests that the amendments addressed to the § 112, second paragraph rejections would in fact reduce or simplify the issues for appeal, as they would have eliminated some or all of the claim rejections under § 112, second paragraph. In accordance with MPEP § 1207, Appellant requests reconsideration and entry of the amendment.

1. The meaning of "HLA" is Clear

The Final Action asserted at ¶ 27 that claims 1, 13 and 19 are indefinite for their recitation of "HLA." Appellant asserts that the meaning of "HLA" is quite clear, as that abbreviation is defined at pg. 2, lines 24-25 as "human leukocyte antigen (HLA)."

2. The meaning of "HLA genetic coding locus" is Clear

The Final Action asserted at ¶ 28 that, "[c]laims 1, 13 and 19 are indefinite with respect to just what constitutes the 'HLA genetic coding locus.'" The Final Action states that, "a locus, by definition, must already comprise a coding region" and asserts that, "it is unclear as to how a genetic coding locus is to be differentiated from a coding locus, or with simply a locus." [Final Action at ¶ 28]

As acknowledged in the Final Action, the Specification at pg. 11, lines 3-9 states that, "an HLA locus is the region of the genomic DNA that includes the gene that encodes an HLA gene product." The Specification at pg. 11, lines 3-7 defines the term "genetic locus" as, "the region of the genomic DNA that includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." Thus, the meaning of "an HLA genetic...locus" is clear from the Specification. The Final Action appears to assert that the insertion of the word "coding" into the phrase "an HLA genetic...locus" renders that phrase indefinite and raises the question of how "an HLA genetic locus" differs from "an HLA genetic coding locus."

According to the definitions of terms in the Specification, there is no difference between "an HLA genetic locus" and "an HLA genetic coding locus," as a "genetic locus" is defined to "include the gene that encodes a protein..." Therefore, since the meaning of "an HLA genetic locus" is clear from the Specification, the metes and bounds of "an HLA genetic coding locus" would be readily apparent to the skilled artisan. Appellant notes that an amendment after final to remove the words "genetic coding" from the phrase "an HLA genetic coding locus" was refused entry as not materially reducing or simplifying the issues for appeal.

3. The phrase "the coding region of the locus" does not lack antecedant basis.

The Final Action asserts at ¶ 29 that the phrase "the coding region of the locus" lacks antecedent support. However, "[t]his form paragraph should ONLY be used in aggravated situations where the lack of antecedent basis makes the scope of the claim indeterminate." [MPEP § 706.03(d)] Obviously, "the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. *Ex parte Porter*, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992).... Inherent components of elements recited have antecedent basis in the recitation of the components themselves." [MPEP § 2173.05]

Appellant asserts that antecedent basis for "the coding region of the locus" is found in the claim 1 recital of "human HLA genetic coding locus." As discussed above, the Specification at pg. 11, lines 3-7 defines the term "genetic locus" as, "the region of the genomic DNA that

includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." It follows from the definition of "genetic locus" that the presence of a "coding region of the locus" is inherent in the recitation of a "human HLA genetic coding locus." Thus, the "coding region of the locus" would consist of the region of the HLA genetic coding locus that "encodes a protein." Such a meaning would be clear to the skilled artisan and the phrase is therefore not indefinite. Appellant notes that an amendment after final to change "the coding region of the locus" to "a coding region of the locus" was refused entry as not materially reducing or simplifying the issues for appeal.

As for the question of whether "the coding region of the locus" would "encompass coding regions (exons) of other genes that are in genetic linkage with the locus" (Final Action at ¶ 29), Appellant fails to see any basis in the claim language or the Specification to support such a construction. The claim clearly recites "the coding region of the locus," not "the coding region of any gene in genetic linkage with the locus." The definition of "genetic locus" in the specification would also appear inconsistent with the Examiner's suggested construction, as it recites, "the region of the genomic DNA that includes the gene that encodes a protein including any upstream or downstream transcribed non-coding regions and associated regulatory regions." There is no recitation relevant to all genes in genetic linkage with the locus.

D. The Examiner Failed to Establish a *Prima Facie* Case of Obviousness to Support a Rejection Under 35 U.S.C. § 103(a).

The examiner bears the initial burden of establishing a *prima facie* case of obviousness [MPEP § 2142]. A *prima facie* case of obviousness requires: [1] some suggestion or motivation, either in the cited references or in the knowledge generally available in the art, to modify the reference or combine reference teachings; [2] a reasonable expectation of success in achieving the claimed invention; and [3] the prior art reference(s) must teach or suggest all the elements of the claimed invention. [*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)] As discussed below, the Examiner has failed to provide factual support for each of the three requirements of a *prima facie* case of obviousness. In addition, the cited references actually "teach away" from the claimed methods.

1. *No suggestion or motivation to combine the reference teachings was present in the cited references or in the knowledge generally available in the art.*

In rejecting claims under 35 U.S.C. § 103, the cited references, must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination, without the benefit of impermissible hindsight afforded by the claimed invention. [MPEP § 2141] As discussed in the following section (2), not only do the cited references lack any suggestion of the desirability of making the claimed combination, but when considered as a whole they teach away from the claimed combination.

The Final Action states that, "Erlich, abstract, teaches a method for performing HLA typing..." but, "does not teach performing an amplification step." [Final Action at ¶¶ 34 and 37] The Final Action asserts that, "Woo et al., page 7, teaches performing an analysis of sample DNA where mutations in non-coding and coding regions are evaluated. In particular, the mutation associated with phenylketonuria (PKU; applicant's claim 7)." [Final Action at ¶ 38] Woo et al. is also said to, "teach combining polymerase chain reaction with the method of nucleic acid analysis as such allows for detection of point mutations with greater ease as well as analysis of minute quantities of DNA." [Final Action at ¶ 40] The Final Action then asserts that, "In view of the teachings of the prior art, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Erlich with the amplification and detection method of Woo et al., so as to allow for the analysis of greater number of human HLA loci and the facile determination of mutations associated with a disease, or with an individual as it relates to paternity testing." [Final Action at ¶ 42]

The Final Action provides no citation to the prior art of record that suggests the desirability of making the claimed combination. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination." [MPEP § 2143.01, citing *In re Mills*, 916 F.2d 680, USPQ2d 1430 (Fed. Cir. 1990] Rather than providing an explicit suggestion in the prior art of the desirability of making the claimed combination, the Examiner asserts without any evidentiary support that, "In view of the teachings of the prior art, it would have been obvious...to have modified the method of Erlich with the amplification and detection method of Woo *et al.*...." [Final Action at ¶ 42]

Reliance on common knowledge in the art requires substantial evidence in support of the Examiner's conclusion. [MPEP § 2144.03] "Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well known. [*Id.*, citing *In re Ahlert,* 424 F.2d 1088, 1091, USPQ 418, 420 (CCPA 1970)] "It is never appropriate to rely solely on 'common knowledge' in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based." [*Id.,* citing *In re Zurko,* 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001)] Appellant respectfully asserts that the Examiner's conclusion that "in view of the teachings of the prior art" it would have been obvious to combine Erlich with Woo et al., is without any documentary support in the cited prior art. The simple fact that it would have been possible to combine Erlich with Woo et al., without some suggestion of the desirability of such a combination, is insufficient to establish a *prima facie* case of obviousness.

2. *The Final Action fails to establish a reasonable expectation of success in achieving the claimed invention.*

A *prima facie* case of obviousness requires that the establishment of a reasonable expectation of success in achieving the claimed invention. [*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)] The reasonable expectation of success must be found in the cited prior art, not in the applicant's disclosure. [*Id.*]

A reasonable expectation of success has been found in the biological arts where a prior art reference, "contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful." [MPEP § 2143.02, citing *In re O'Farrell,* 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988] In the instant case, all three factors found in *O'Farrell* to support a conclusion of reasonable expectation of success are missing.

First, there is no "detailed enabling methodology" disclosed in the cited prior art. The sole disclosure relevant to polymerase chain reaction amplification is a prophetic example in Woo et al. (pages 24-27). That example provides only general guidance to the skilled artisan as to how to perform PCR amplification, with no disclosure of how such a technique might be applied to HLA loci. The Final Action takes the position that amplification primers and amplification conditions specific for HLA loci are required for enablement [*see* Final Action at

¶¶ 20-24] Neither Woo *et al.*, nor Erlich provide any HLA primer sequences or amplification conditions for HLA loci. In contrast, the instant application discloses, according to the Final Action (¶ 16), primers specific for the HLA-A, HLA-B, HLA-C, Class I, HLA-DQA1, HLA-DRA, HLA-DRB, HLA-DQB1 and HLA-DPB1 loci. In fact, the instant application discloses fifty-eight specific HLA primer sequences (SEQ ID NO's 30-87), compared to zero HLA primers disclosed in the cited prior art. The instant application further provides numerous specific examples of the actual amplification and analysis of non-coding sequences from HLA loci, compared to a single prophetic example of Woo et al. Specifically, Woo *et al.*, at pg. 25, 2nd paragraph state:

> One microgram of human DNA, 1 μM of each oligonucleotides and 1.5 mM of each deoxynucleotide triphosphate in 10 mM tris-chloride is heated at **100°C** for 5 minutes and cooled in an **ice bath**. Five units of Klenow fragment is added and the reaction is incubated at **25°C** for 2 minutes. The cycle of heating, cooling, adding enzyme and reacting is repeated twenty times. (emphasis added)

Appellant asserts that the person of ordinary skill, as of the instant application's priority date, would have been aware that the temperature conditions disclosed by Woo *et al.*, were generally unsuitable for PCR amplification. For comparison, the instant application at pg. 79, lines 1-11 disclosed standard PCR amplification conditions:

> Each amplification reaction mixture is heated to 94°C for 30 seconds. The primers are annealed to the sample DNA by cooling the reaction mixtures to 65°C for each of the A locus-specific amplification mixtures and to 55°C for each of the DQA1 locus-specific amplification mixtures and maintaining the respective temperatures for one minute. The primer extension step is performed by heating each of the amplification mixtures to 72°C for one minute. The denaturation, annealing and extension cycle is repeated 30 times for each amplification mixture.

In the absence of enabling details concerning any primer sequences, along with marginal disclosure of amplification conditions, Appellant asserts that the cited prior art failed to disclose enabling methodology sufficient to provide a reasonable expectation of success in achieving the claimed invention.

As noted previously, no suggestion to modify the prior art, nor any evidence suggesting the modification would be successful, is cited by the Final Action. In fact, the cited prior art taught away from the claimed combination, by leading the skilled artisan to believe that the RFLP analysis used by Erlich for HLA typing was undesirable, compared to the direct detection

of causal mutations by DNA sequencing and/or probe hybridization used by Woo *et al.* Woo *et al.*, state at pg. 4, 1st paragraph that:

> These methods of heterozygote detection require the ascertainment of a family through a proband. Furthermore, they require family studies in order to determine the segregation of the PKU alleles with restriction fragment length polymorphisms (RFLP) at the phenylalanine hydroxylase (PAH) locus. Even with family studies, the extensive RFLP's identified in the human phenylalanine hydroxylase locus still leaves some families without a method for detection of heterozygosity or for prenatal diagnosis of affected PKU individuals. The present invention is directed to a new an improved use of molecular biology technology to measure the actual mutations in the PAH locus.

Thus, far from suggesting the claimed combination, the cited prior art actually taught away from the claimed combination, suggesting that the direct measurement of causal mutations was superior to indirect detection of linked RFLP sites. Considering the cited prior art references as a whole, in the absence of any suggestion to make the claimed combination, along with a teaching away from the claimed combination, renders the combination of references improper and fails to provide a reasonable expectation of success in achieving the claimed combination.

3. The Final Action fails to assert that the cited prior art teach or suggest all the elements of the claimed invention.

Nowhere does the Final Action assert that either Woo or Erlich teach the element of "using the one or more non-coding region sequence variations [detected in an amplified genomic DNA sequence] to determine at least one haplotype encompassing [a] human HLA genetic coding locus," as recited in pending Claim 1. Rather, the Final Action asserts that it would have been obvious to have modified the method of Erlich with the method of Woo *et al.*, to allow for the "determination of mutations associated with a disease, or with an individual as it relates to paternity testing." [*Id.*] However, the pending claims do not contain any recitation of, "determination of mutations associated with a disease, or with an individual as it relates to paternity testing." Rather, the claims clearly refer to determining haplotypes encompassing HLA loci. As the Final Action fails to assert that the element of "using the one or more non-coding region sequence variants to determine at least one haplotype encompassing a human HLA locus is disclosed in either cited reference, a *prima facie* case of obviousness has not been established.

CONCLUSION

Appellant respectfully asserts that each of the rejections set forth in the Final Action is improper. The rejections under 35 U.S.C. § 112, first paragraph for lack of written description and lack of enablement are based on a flawed construction of claim scope, that is inconsistent with the interpretation that those skilled in the art would reach, considering the clear language of the claims and the further disclosure of the Specification. Appellant asserts that there is ample written description support in the Specification, commensurate with the properly construed scope of the claims, and that the disclosure in the Specification, in consideration of general knowledge in the prior art, provides ample enablement support. Although the Examiner should properly have entered the requested amendment after Final Action, which would have addressed all outstanding § 112, second paragraph issues, Appellant asserts that the meaning of the presently pending claims would be clear to the skilled artisan.

As discussed above, since the Examiner failed to establish a *prima facie* case of obviousness, including a lack of support for each of the three *In re Vaeck* factors required for a *prima facie* case, the rejection of claims under 35 U.S.C. § 103 was also improper.

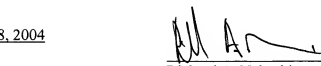
Appellant respectfully requests that: (a) the previously submitted amendment after final be entered in the case; and (b) reversal of the Examiner's rejections and allowance of the pending claims.

The appropriate fee of $330.00 for the filing and consideration of this Appeal Brief is enclosed. Should any additional fee be required, the Commissioner is authorized to charge our Deposit Account No. 06-0029 and requested to notify us of same.

Respectfully submitted,

FAEGRE & BENSON LLP

Date: September 28, 2004



Richard A. Nakashima
Reg. No. 42,023

2200 Wells Fargo Center
90 South Seventh Street
Minneapolis, MN 55402-3901
(303) 447-7728

APPENDIX A

37 C.F.R. § 1.192(c)(9)

The claims on appeal read as follows:

Claim 1. (previously presented) A method of determining at least one haplotype encompassing a human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA, wherein the amplified genomic DNA comprises a non-coding region sequence that is in genetic linkage with an HLA genetic coding locus;

(b) detecting one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

Claim 2. (original) The method of claim 1, wherein a single haplotype is determined.

Claim 3. (original) The method of claim 1, wherein two or more haplotypes are determined.

Claim 4. (canceled)

Claim 5. (original) The method of claim 1, wherein the at least one haplotype is associated with a genetic disease.

Claim 6. (original) The method of claim 5, wherein the disease is cystic fibrosis.

Claim 7. (original) The method of claim 5, wherein the disease is phenylketonuria, muscular dystrophy or beta-thalassemia.

Claim 8. (previously presented) The method of claim 1, further comprising

(i) detecting one or more sequence variations in the coding region of the locus; and

(ii) using the one or more coding region sequence variations to determine at least one haplotype encompassing the human HLA genetic coding locus.

Claim 9. (previously presented) The method of claim 1, further comprising:

(a) analyzing DNA from a crime scene sample;

(b) analyzing DNA from a sample of a suspected perpetrator of the crime; and

(c) comparing the haplotypes present in the crime scene sample and the suspected perpetrator sample.

Claim 10. (canceled)

Claim 11. (previously presented) The method of claim 1, further comprising:

(a) analyzing DNA from an off-spring;

(b) analyzing DNA from at least one suspected parent; and

(c) comparing the haplotypes present in the offspring's DNA and in the suspected parent's DNA.

Claim 12. (original) The method of claim 1, wherein the amplified genomic DNA further comprises at least part of at least one exon.

Claim 13. (previously presented) A method for determining at least one haplotype encompassing a multi-allelic human HLA genetic coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA genetic coding locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said at least one haplotype;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the multiallelic human HLA genetic coding locus.

Claim 14. (original) The method of claim 13, wherein a single haplotype is determined.

Claim 15. (original) The method of claim 13, wherein two or more haplotypes are determined.

Claim 16. (canceled)

Claim 17. (original) The method of claim 13, wherein the at least one haplotype is associated with a genetic disease.

Claim 18. (original) The method of claim 17, wherein the genetic disease is associated with variations in a regulatory or other untranslated region of the genetic locus.

Claim 19. (previously presented) A method for determining at least one haplotype encompassing a human HLA coding locus comprising:

(a) amplifying human genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said HLA coding locus;

(b) analyzing the amplified DNA sequence to detect one or more sequence variations in the non-coding region; and

(c) using the one or more non-coding region sequence variations to determine at least one haplotype encompassing the human HLA coding locus.

Claim 20. (original) The method of claim 19, wherein a single haplotype is determined.

Claim 21. (original) The method of claim 19, wherein two or more haplotypes are determined.

Claim 22. (canceled)

Claim 23. (previously presented) The method of claim 19, further comprising:

(a) analyzing DNA from a crime scene sample;

(b) analyzing DNA from a sample of a suspected perpetrator of the crime; and

(c) comparing the haplotypes present in the crime scene sample and the suspected perpetrator sample.

Claim 24. (canceled)

Claim 25. (previously presented) The method of claim 19, further comprising:

(i) analyzing DNA from an off-spring;

(ii) analyzing DNA from at least one suspected parent; and

(iii) comparing the haplotypes present in the offspring's DNA and in the suspected parent's DNA.

Claim 26. (previously presented) The method of claim 1, wherein the haplotype is determined by detecting polymorphisms in coding and non-coding regions.

Claim 27. (previously presented) The method of claim 1, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claim 28. (previously presented) The method of claim 13, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claim 29. (previously presented) The method of claim 19, wherein the haplotype is determined by detecting polymorphisms in coding and non-coding regions.

Claim 30. (previously presented) The method of claim 19, wherein the non-coding region comprises an intervening sequence, a 5' untranslated sequence (5'-UTR), a 3'-UTR, a regulatory sequence or an intergenic sequence.

Claims 31-46. (canceled)